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REVIEW ARTICLE

AN ITINERARY TO ACCESS THE COLON

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ABSTRACT:

Although oral delivery has become a widely accepted route of administration of therapeutic drugs, the gastrointestinal tract presents several formidable barriers to drug delivery. The delivery of drugs to the colon has a number of important implications in the field of pharmacotherapy. Drugs that are destroyed by the acidic environment of the stomach or metabolized by pancreatic enzymes are only slightly absorbed in the colon. Targeted delivery of drugs to the colon has attracted much interest recently for local treatment of a variety of colonic diseases such as irritable bowel syndrome (IBS), colorectal cancer and inflammatory bowel diseases (IBD), which includes both ulcerative colitis and crohn's disease. The colon is also receiving significant attention as a portal for the entry of drugs into the systemic circulation. A variety of delivery strategies and systems have been proposed for colonic targeting.This article shall review the diverse strategies used to target the drug to the colon.The various features of different approaches allowing locally restricted drug delivery to the inflamed colon are discussed including the main physiological issues and histological changes of the colon as its cancer develops.

Key words: Challenges and approaches in colon targeting, inflammatory bowel disease

INTRODUCTION

Oral colon-specific drug delivery systems have recently gained importance for delivering a variety of therapeutic agents. The major obstacles in delivering drugs to the colon are the absorption and degradation pathways in the upper gastrointestinal tract. However, a successfully designed colon-targeted system can overcome these obstacles. Colon targeting has proven beneficial for local action in a variety of disease conditions, such as inflammatory bowel disease, irritable bowel syndrome and colonic cancer. Colon targeting has also proven useful for systemic action of protein-peptide drugs such as insulin, calcitonin, and met-enkaphalin and even for other nonpeptide drugs such as cardiovascular and antiasthmatic agents[1].

Oral colon delivery is currently considered important not only for the treatment of local pathologies, such as primarily inflammatory bowel disease (IBD), but also as a means of accomplishing systemic therapeutic goals. Accordingly, it has been under extensive investigation as a possible strategy to improve the oral bioavailability of peptide and protein drugs[2].This manuscript brings to account various approaches for targeting orally administered dosage forms to the colon and physiological issues encountered during targeting.

1.1 Challenges in the colon targeting of drugs: A drug formulation when moves from mouth to colon encounters various physiological and histological challenges. Also, drug absorption from the colon has its own limitations and are discussed below.

1.1.1 Physiological issues:

a) pH: The most common physiological factor considered in the design of delayed release colonic formulations is pH gradient of the GIT. It is highly desirable for pH-dependent colonic formulations to maintain their physical and chemical integrity during passage through the stomach and small intestine and reach the large intestine where the coat should disintegrate to release the drug locally. It should however be noted that GI fluids might pass through the coat while the dosage form transits through the small intestine. This could lead to premature drug release in the upper parts of GIT and as a result loss of therapeutic efficacy may occur. To overcome these problem higher coating levels of enteric polymers is to be applied. However, this also allow sinflux of GI fluids through the coat and the thicker coat soften rupture under the influence of contractile activity in the stomach[3].The pH of different regions of GIT are shown in Figure 1.

b) Enzymes: The human colon is a dynamic and ecologically diverse environment, containing over 400 distinct species of bacteria witha population of 10^{11} to 10^{12} CFU/mL with bacteroides, bifidobacterium, eubacterium, lactobacillus etc., greatly out numbering other species.These bacteria produce a wide spectrum of enzymes that, being reductive and hydrolytic in nature, are actively involved in many processes in the colon, such as carbohydrate and protein fermentation, bile acid and steroid transformation, metabolism of xenobiotic substances, as well as the activation and destruction of potential mutagenic metabolites[4]. Figure 2 enlists various reductive and hydrolytic enzymes in colon.

c) Motility of colon/ Transit time: The transit time is highly variable and influenced by a number of factors like diet (in particular, dietary fiber content), mobility, stress, drugs, and disease status. Colonic transit times ranged from 50 to 70 hours[5]. Colonic contractile activity can be described by irregular alternation of quiescence, prevalence of non-propagating, segmental contractions and infrequent occurrence of propagated contractions that can be further classified into low amplitude (the amplitude <50

mmHg) and high amplitude propagated contractions (the amplitude >100 mmHg). The occurrence of low amplitude propagated contractions is rather frequent (on an average, more than 100 times per day) and high amplitude propagated contractions are reported to be in the range of 4 to 12 times per day in healthy subjects, usually upon awakening in the morning and post prandial[6].

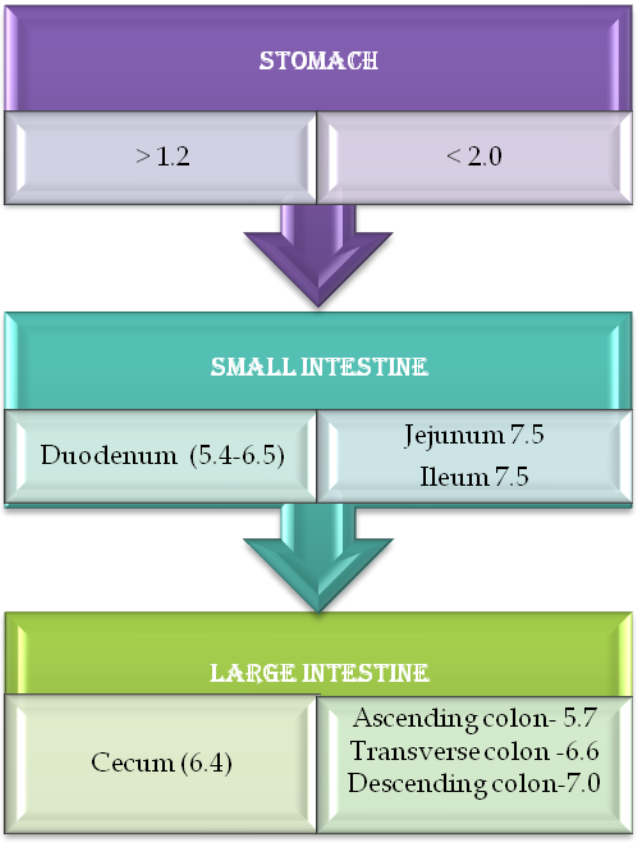

Figure 1: pH in different regions of GIT

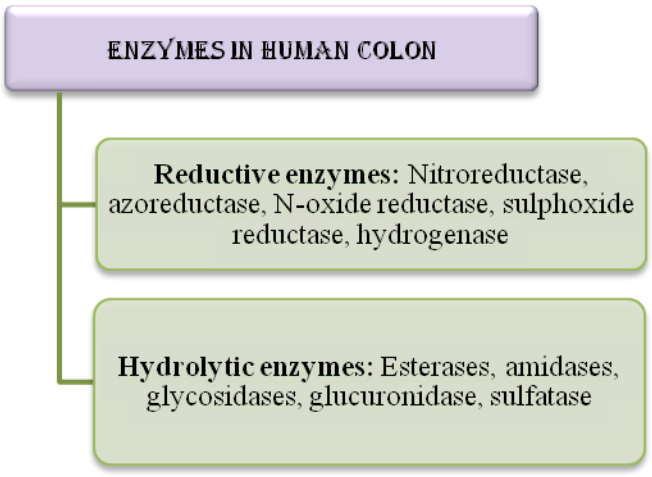

Figure 2: List of reductive and hydrolytic enzymes in colon

d) Drug release rate/ drug dissolution: It is thought to be decreased in the colon, which is attributed to the fact that less fluid is present in the colon than in the small intestine[7]. The poor dissolution and release rate may in turn lead to lower systemic availability of drugs. These issues could be more problematic when the drug candidate is poorly water-solubleor require higher doses for therapy. Consequently, such drugs need to be delivered in a presolubilized form or formulation and then should be targeted for proximal colon, which has more fluid than in the distal colon[8]. Likewise, colonic formulations for polar drugs including proteins and peptides require use of absorption enhancing agents (also known as absorption promoters).

e) Biodegradation: The primary source of nutrition for these anaerobic bacteria is carbohydrates such as non-starch polysaccharides (i.e. dietary fibers) from the intestinalchime. It is well established that non-starch polysaccharides are fermented during transit through the colon and the break down in the stomach and small intestine is negligible. Enzymes responsible for the degradation of polysaccharides include α-larabinofuranosidase, β-D-fucosidase, β-D-galactosidase, β-Dglucosidase, β-xylosidase, with the last three enzymes being the most active[4].

f) Disease status of colon: An immediate issue for targeted delivery systemsis site of the disease in the patient. IBD is comprised of two specific conditions: ulcerative colitis (UC) and crohn's disease (CD). In UC, sites of inflammation extend to the more proximal regions of the colon over time. In CD, the predominant site of inflammation is the distal ileum; between 30% and 40% of patients also have significant colonic involvement[9]. Figure 3 summarizes all the physiological barriers encountered while targeting drugs to colon and Table 1 shows the various drugs used in IBD.

g) Barriers in colonic absorption: In the lumen itself, specific and nonspecific drug binding occurs through the interaction of the drug with dietary components[10]. Non selective interactions could occur between regions of the glycoprotein drug and undigested food stuffs such as waxes and alginates. The mucus layer at the epithelial surface, due to it's highly charged and sieve like nature presents a formidable thermodynamic barrier to the transit of large, negatively charged drug molecules. Cephalosporins, penicillins and aminoglycosides are few examples of small molecule drugs that can bind to negatively charged mucus[11]. This might facilitate longer colonic residence time and hence environmental or enzymatic degradation. Although removal of the mucus barrier using mucolytic agents might seem attractive, this may implicate in a variety of disease processes and pathological conditions due to alteration of intact mucus layer. Another barrier to colonic absorption particularly for the lipophilic drugs is unstirred water layer present between the space of mucus layer and epithelial cells.

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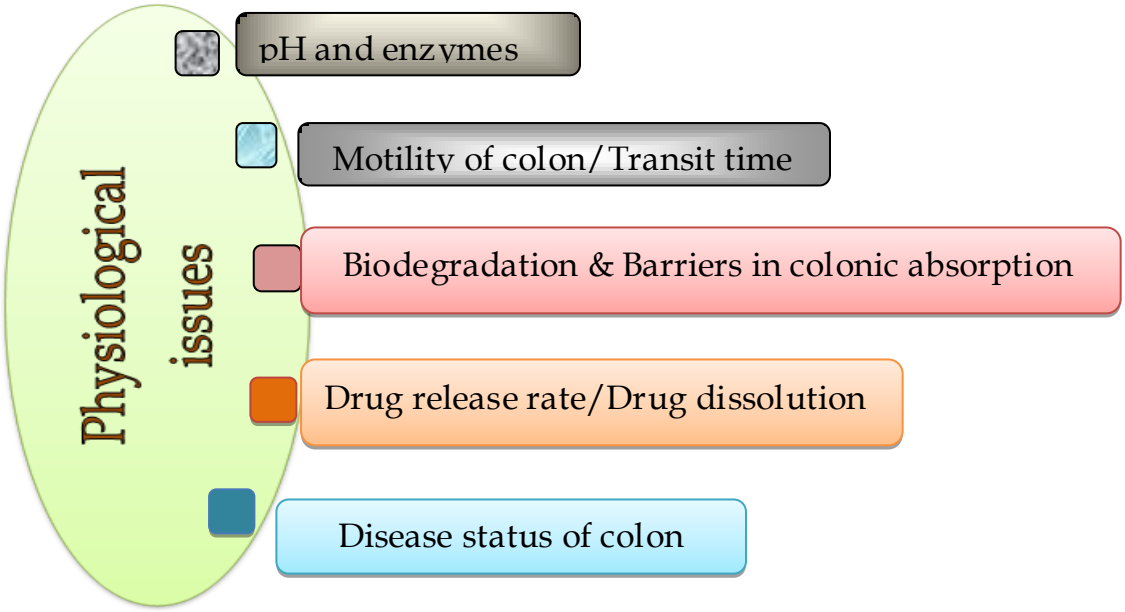

Figure 3: Summary of physiological barriers encountered while targeting drugs to colon

Table 1: Various drugs used in inflammatory bowel disease

Status of disease	Drug used	Ref
Ulcerative colitis	Glucocorticosteroid Salicylates Infliximab	12 13 14
Crohn's disease	Clarithromycin, rifabutin, and clofazimin Tacrolimus Adalimumab	15 16 17
Irritable bowel syndrome	Renzapride Asimadoline Tegaserod Maleate	18 19 20
Colorectal cancer	Oxaliplatin, capecitabine, Bevacizumab, irinotecan	21 22
Diverticulitis of colon	Mesalazine and rifaximin	23

1.1.2Histopathological issues: Various stages of colon cancer are discussed in Table 2

Table 2: Stages of colon cancer[24]

Stage 0	Intraepithelial or invasion of the lamina propria, no regional lymph node metastasis, no distant metastasis.
Stage I	Tumour invades submucosa; tumour invades muscularispropria, no regional lymph node metastasis, no distant metastasis.
Stage II A	Tumour invades through the muscularis propria into the subserosa, or into the nonperitonealizedpericolic or perirectal tissues, no regional lymph node metastasis, no distant metastasis.
Stage II B	Tumour directly invades other organs or structures and/or perforates the visceral peritoneum, no regional lymph node metastasis, no distant metastasis.
Stage III A	Tumour invades submucosa; tumour invades muscularis propria, metastasis in regional lymph nodes, no distant metastasis.
Stage III B	Tumour invades through the muscularis propria into the subserosa, or into the nonperitonealized pericolic or perirectal tissues, tumour directly invades other organs or structures and/or perforates the visceral peritoneum, metastasis in regional lymph nodes, no distant metastasis
Stage III C	Tumour directly invades other organs or structures and/or perforates the visceral peritoneum , metastasis in more regional lymph nodes,no distant metastasis
Stage IV	Tumour directly invades other organs or structures and/or perforates the visceral peritoneum,metastasis in more regional lymph nodes, distant metastasis

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2.1 Approaches to colon specific drug delivery

A variety of approaches have been used and systems[25]have been developed for the purpose of achieving colonic targeting. These are included in Figure 4:

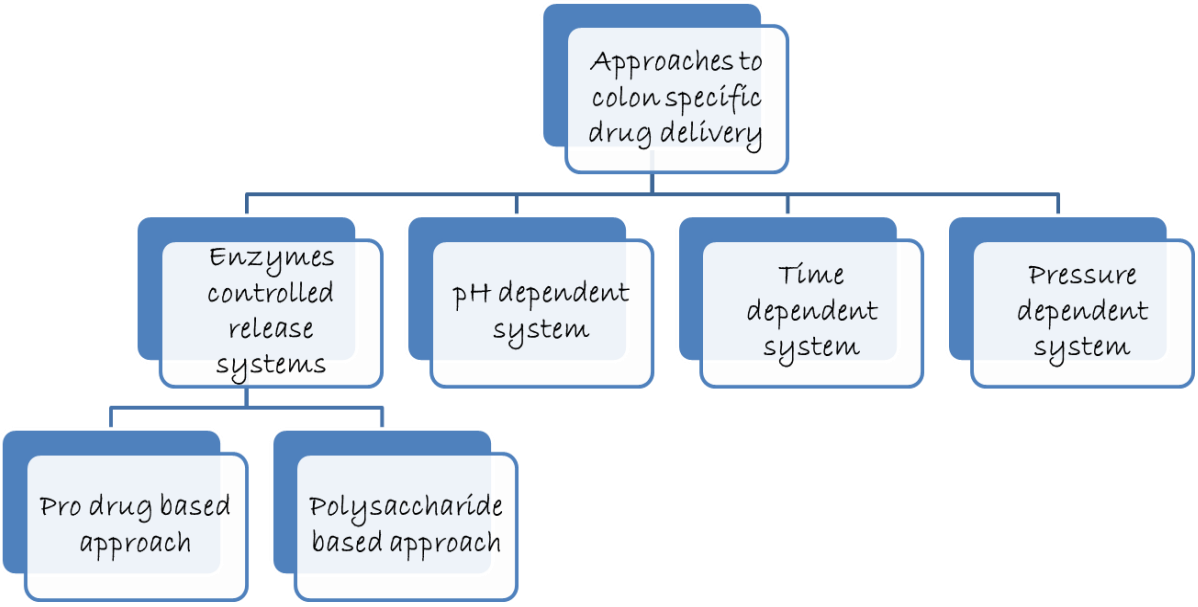

Figure 4: Approaches to colon specific drug delivery

1. Systems developed with pH sensitive polymer: The pH in the gastrointestinal tract varies widely [26].Use of pH-dependent polymers is based on the differences in pH levels. The polymers described as pH-dependent in the colon specific drug delivery systems are insoluble at low pH levels but become increasingly soluble as pH rises. It is highly desirable for pH-dependent colonic formulations to maintain their physical and chemical integrity during passage through the stomach and small intestine and reach the large intestine where the coat should disintegrate to release the drug locally[27].

2. Time dependent systems: Time-controlled formulations for colonic delivery are also delayed-release formulations in which the delay indelivery of the drug is time-based. In these systems, the site of drug release is decided by the transit time of a formulation in the GI tract, which makes it challenging to develop a formulation in order to achieve a precise drug release in the colon. Ideally, formulations are designed such that the site of delivery (i.e. colon) is not affected by the individual differences in the gastric emptying time, pH of the stomachand small intestine or presence of anaerobic bacteria in the colon [28].

The drug release from these systems therefore occurs after a predetermined lag phase, which is precisely programmed by selecting a suitable combination of controlled-release mechanisms. In general, time-controlled formulations for colonic delivery include apH-dependent (enteric coat) component because the transit of a formulation in the GI tract is largely influenced by the gastric emptying time. Enteric coating is also used for preventing the rapid swelling and disintegration in upper GIT since other controlled-release components based on mechanism of swelling (gelling), osmosis or a combination of two are often included in the time-release formulations [27].

3. Enzyme controlled release systems: Microflora activated delivery systems are considered to be preferable and promising since the abrupt increase of the bacteria population and associated enzymatic activities in ascending colon represents a non-continuous event independent of GI transit time and pH [4].

a) Prodrug approach: Prodrug activation may be accomplished by the utilization of some specific property at the target site, such as altered pH or high activity of certain enzymes relative to the non-target tissue, for the prodrug-drug conversion [29].When synthesizing prodrugs, the choice of carrier depends on the functional group available on the drug molecule for conjugation with the carrier (e.g., the hydroxyl group present on the corticosteroids can enter into a glycosidic linkage[30]with various sugars,the carboxyl group of biphenylyl acetic acid forms anester/amide conjugate with cyclodextrin etc[31].

I. Amino-acid conjugates: Proteins and their basic units [i.e. the amino-acids (A.A.)] have polar groups like the $-NH_2-$ and $-COOH-$. These polar groups are hydrophilic and reduce the membrane permeability of A.A and proteins [32].

II. Glycoside conjugates: Certain drugs can be conjugated to different sugar moieties to form glycosides. The drug part forms the aglycone andis linked to the sugar part, which forms the glycone part of the glycoside [30].

III. Glucuronide and sulphate conjugates: Glucuronide and sulphate conjugation are the major mechanisms for the inactivation and preparation for clearanceof a variety of drugs. Bacteria of the lower GIT, however, secrete β-glucuronidase and can deglucuronidate avariety of drugs in

the intestine. Thus, the deglucuronidation process results in the release of the active drug again and enables its reabsorption[33].

IV Azo-conjugates: The use of these azo compounds forcolon-targeting has been in the form of hydrogels as a coating material for coating the drug cores and as prodrugs[34]. In the colon, the azoreductases cleave the azo bond releasing the drug, 5-ASA and the carrier sulphapyridine (SP). Due to side effects of SP, another approach was used which was based on joining two molecules of 5-ASA together to form an ultimate prodrug, disodium azodisalicylate (olsalazine), in which one moleculeof 5-ASA is used as a carrier for the other[29].

V Polymeric prodrugs: Polymeric prodrugs with drug molecule linked directly toa high molecular weight polymeric backbone. For example the α and β-cyclodextrins are practically resistantto gastric acid, salivary, and pancreatic amylases. Aclinical study has shown clear evidence that β-cyclodextrin is poorly digested in the small intestine but is almost completely degraded by the colonic microflora[35]. In another example cyclodextrin derivatization with 17-beta estradiol was explored extensively[36] by Kim et al., 2010. Table 3and 4 shows some of prodrugs and their colon specific drug delivery.

VI Polysaccharide based approach: The colonicbacteria are predominately anaerobic in nature andsecrete enzymes that are capable of metabolizing substrates such as carbohydrates and proteins that escapethe digestion in the upper GIT[37]. Polysaccharides, the polymer of monosaccharide retain their integrity because they are resistant to the digestive action of gastrointestinal enzymes [38]. The matrices of polysaccharides are assumed to remain intact in thephysiological environment of stomach and small intestine but once they are acted upon by the bacterial polysaccharidases that results in the degradation of the matrices[39]. Limitations associated with the use of polysaccharides as drug carriers for colonic delivery are that these materials are hydrophilic in nature so they must be made water insoluble by cross linking or hydrophobic derivatisation[40]. Table 5 enlists a number of polysaccharides used for the colon drug delivery.

Table 3: Prodrugs evaluated for colon specific drug delivery and their in vitro/in vivo performance

Carrier	Drug investigated	Linkage hydrolysed	Model(s) used	Ref
Saccharide carriers				
Glucose	Dexamethasone	Glycosidic linkage	Guinea pig	47
Glycosylated nanocarriers	Genes	Glycosidic linkage	In vitro	48
Amino acid conjugates				
Tyrosine/methionine	Salicylic acid	Amide linkage	Rabbit	49
L/D-Alanine	Salicylic acid	Amide linkage	In vitro	50
19 amino acid conjugates of abscisic acid	Abscisic acid	Amide linkage	In vitro/In plant	51
Azo conjugates				
Sulphapyridine	5-ASA	Azo-linkage	Man	52
p-Aminobenzoyl -β- alanine	5-ASA	Azo-linkage	Man	53
Polyurethanes with azo aromatic groups	Fluoreceinisothiocynate	Azo-dextran linkage	In vitro	54
Azo-dextran polymer	Rhodamine, Aspirin	Azobenzene (N=N trans−cis isomerization	In vitro	55
Azo linkage with sulphasalazine	5-ASA with essential amino acids	Azo- linkage	In vitro Rat	56
Glucuronide conjugates				
Glucuronic acid	Naloxone/ Nalmefene	Glucuronide linkage	Rat	57
Methyl 1-O-trichloroacetimidoyl-2,3,5-tri-O-isobutyryl-α-d-glucopyran-uronate	Soraprazan	Glucuronide linkage	In vitro	58

4. Pressure dependent systems: Viscosity of the luminal contents within the colon is greater than at other sites within the GIT due to the reabsorption of water from the large intestine. This change in viscosity leads to an increase in pressure resulting from the peristaltic forces. This pressure change can be used to trigger drug release [41].

a) Osmotic Controlled Drug Delivery (ORDS-CT): Push-pull OROS-CT system comprises of 5 push-pull units encapsulated within a hard gelatin capsule. Each push pull unit is a bilayered laminated structure containing an osmotic push layer and a drug layer, both surrounded by a semipermeable layer. An orifice is laser drilled into the semipermeable membrane to the drug layer. The outside surface of the semipermeable membrane is then coated by Eudragit S-100 to delay the drug release from the device during its transit through the stomach. Upon arrival in the small intestine, the coating dissolves at a pH ≥7. As a result, water enters the unit causing the osmotic push compartment to swell forcing the drug out of the orifice into the colon. The drug release kinetics is precisely controlled by the rate of influx of water through the semipermeable membrane [42,43].

b) Pressure-controlled colon delivery capsule (PCDC): It is made up of ethyl cellulose that has been developed to target the drugs to the colon. The PCDC is composed of drug, dispersed in a suppository base, and coated with hydrophobic polymer and ethyl cellulose. Once swallowed, the temperature of the body causes the suppository base to melt and increase in volume and the system resembles a liquid-filled ethyl cellulose balloon.

The balloon is able to withstand the luminal pressure of the small intestine resulting from peristalsis, but will rupture when subject to the pressure of more intense contractions of the colon and contents of thicker viscosity [44].

Novel Colon Targeted Delivery System (CODESTM): CODESTM is a unique CDDS technology that was designed to avoid the inherent problems associated with pH or time dependent systems[45]. CODESTM is a combined approach of pH dependent and microbially triggered CDDS. It has been developed by utilizing a unique mechanism involving lactulose, which acts as a trigger for site specific drug release in the colon. The system consists of a traditional tablet core containing lactulose, which is over coated with and acid soluble material, Eudragit E, and then subsequently overcoated with an enteric material, Eudragit L. The premise of the technology is that the enteric coating protects the tablet while it is located in the stomach and then dissolves quickly following gastric emptying. The acid soluble material coating then protects the preparation as it passes through the alkaline pH of the small intestine. Once the tablet arrives in the colon, the bacteria enzymatically degrade the polysaccharide (lactulose) into organic acid. This lowers the pH surrounding the system sufficient to affect the dissolution of the acid soluble coating and subsequent drug release [46]. The summary of the stratergies are given in Table 6 A and 6 B.

Table 4: Prodrugsevaluated for colon specific drug delivery and their in vitro/in vivo performance(Continued)

Carrier	Drug investgated	Linkage hydrolysed	Model(s) used	Ref
Cyclodextrin conjugates				
Cyclodextrin	Biphenylyl acetic acid	Ester/amide	In vitro	59
β-cyclodextrin-poly (4-acryloyl morpholine)	Acyclovir	Ester linkage	In vitro	60
Polymeric prodrugs				
Poly-L-aspartic acid	Dexamethasone	Amide linkage	Rat	61
Polyamidoaminedendrimer and poly(ethylene glycol) with or without galactose	Doxorubicin	Acid-labile hydrazone linker	In vitro	62
Dextran conjugate				
Dextran	Naproxen	Ester linkage	Rabbit	63
β-lactoglobulin-dextran maillard conjugates	Lipid, proteins	Carbohydrate linkage	In vitro	64

Table 5: Polysaccharides investigated for colon specific drug delivery with their dosage forms and summary of the results obtained

Polysaccharide investigated	Model drug	Dosage form prepared	Model (s) used	Ref
Chitosan	Insulin	Capsules	Rat	65
	Sod.diclofenac	Microspheres	In vitro	66
Pectin	Indomethacin	Matrices	In vitro	67
	Radioactive tracer	Matrix tablets	Man	68
	Resveratrol	Microparticles	In vitro/ rat	69
Guar gum	Trimetazidine dihydrochloride	Guar gum-based three-layer matrix tablets	Man	70
Sugar cane native dextran	Lobenzarit disodium and propranolol hydrochloride	Compressed tablets	In vitro	71
Methacrylated inulin	_	Crosslinked hydrogels	In vitro	72
Chondroitin sulfate	_	Matrix tablet	In vitro	73
Starch	Radioactive tracer	Enteric-coated capsules	Man	74
Amylose/ethyl cellulose (1:4)	Glucose	Coated cores	Man	75

Table 6 A: Summary of formulation evaluation of colon targeting drug delivery systems when various approaches were used

Polymers	Drug investigated	Dosage form	Model (s) used	Performance of the system	Ref
pH dependent system					
Alginate–guar gum hydrogel crosslinked with glutaraldehyde	Protein model (BSA)	Hydrogel	In vitro	Guar gum and glutaraldehyde crosslinking increases entrapment efficiency and prevents the rapid dissolution of alginate in higher pH of the intestine.	76
Diblock copolymers of polyethylene glycol and t-butyl methacrylate, ethyl acrylate or n-butyl acrylate	Indomethacin Fenofibrate	Emulsion	In vitro	Drug release from pH-sensitive supramolecular assemblies increased with pH shift from 1.2 to 7.2. Such pH-sensitive self-assemblies can be potentially useful to enhance the oral bioavailability of poorly water-soluble drugs.	77
Two methacrylic acid copolymers – Eudragit L100 and Eudragit S100.	Tegaserod maleate (TM)	Tablet	In vitro/ beagle dog	The results of the present study have demonstrated that the pH-dependent tablet system is a promising vehicle for preventing rapid hydrolysis in gastric milieu and improving oral bioavailability of TM for the treatment of irritable bowel syndrome.	78
Time dependent system					
Pectin–4-aminothio phenol (Pec–ATP)	Metronidazole (Met)	Microparticl es	In vitro	34.4-fold more (met) is retarded in Pec–ATP microparticles within 6 h compared to control particle.	79
Eudragit NE 30 D (inner coating) &Opadry OY-P-7171 (outer coating)	Sophoraflavesc ensaiton (ASF, extracts	Tablet coated	In vitro/ dog	ASF wax-matrix tablets coated with Eudragit NE 30 D and Opadry OY-P-7171 using the regular coating technique could be designed to achieve a lag time of 3 h in the small intestinal tract.	80
Pectin and chitosan	Metronidazole	Compressio n coated tablet	In vitro/ rat	Selective delivery of metronidazole to the colon could be achieved using a pectin or pectin chitosan mixture in the form of compression coated tablets.	81
Time and pH dependent systems					
Eudragit S-100 and Poly(dl-lactide-co-glycolide) (PLGA)	Budesonide	Microparticl es	In vitro	Application of double microencapsulation technique employing PLGA matrix and Eudragit S-100 coating shows promise for site specific and controlled delivery of budesonide in crohn's disease.	82
Eudragit RS 30D and Eudragit L 55 30D	Indomethacin	Minitablets	In vitro/ human	Absorption of indomethacin from mini tablets with colon release occurs after a lag time of 2.5-3 h.	83
Eudragit L-100 and S-100 (1:2)	Theophylline	Microcapsul es	In vitro/ rat	Pulsatile drug release over a period of 2–24 h, consistent with the requirements for chronopharmaceutical drug delivery was achieved from insoluble gelatin capsules, in which microencapsulated theophylline was sealed by means of a suitable hydrogel plug.	84

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Table 6 B: Summary of formulation evaluation of colon targeting drug delivery systems when various approaches were used

Polymers	Drug	Dosage form	Model used	Performance of the system	Ref
Microflora activated system					
Pectin (PT)	Ketoprofen (KP)	Synthetically dried residue	In vitro/ rat	Enzyme-dependant PT-KP prodrug and the time required to reach the maximum drug level was 8 h.	85
Eudragit FS30D Guar gum	Budesonide	Pellets	In vitro/ rat	Polymer mixture coated formulation also concluded that formulation was found to be stable to acid environment of stomach and formulation was reached to ileocecal junction within 5th h and at 7th h of study the formulation indicating the dissolution of polymer coat in colon to release the drug specifically in colon.	86
Amylose and ethylcellulose	5-amino salicylic acid	Pellets	In vitro/ rat	Digestion of mixed amylose and ethylcellulose films was proportional to the quantity of amylose present in the film. Drug release from coated pellets was accelerated in the presence of the enzyme.	87
Pressure triggered delivery					
Ethyl cellulose film	Caffeine	Pressure-controlled capsule	Man	Thickness of ethyl cellulose film is an important factor in disintegrating of the formulation	88
Ethylcellulose	Caffeine	Pressure-controlled colon delivery capsule (PCDC)	Man/ In vitro	PCDCs disintegrate in the colon due to luminal pressures and peristalsis was evaluated by a PK study involving the salivary excretion of caffeine after oral administration of PCDC to human subjects, the mean thickness of the EC coating membrane was 50±1 µm and of which mean hardness was 2.08±0.15 newton was thought to deliver caffeine into the human colon.	89
Zinc-pectinate	Theophylline	Pulsatile controlled system in form of beads	In vitro / rat	Delayed release was attributed to the formation of a zinc phosphate coating in vitro and in vivo inducing the retention of theophylline release. Zn-pectinate beads exhibit interesting properties due to its potential as pulsatile delivery system induced by the in situ formation of Zn phosphate, while Ca-pectinate was found to be of limited suitability for controlled release of theophylline.	90
Pregelatinized starch and wax	Pentoxifylline and behenic acid	Dry-coated tablet	In vitro	Disintegration time depended on the weight fraction of the core tablet, and the drug release rate after disintegration increased with increasing drug concentration in the core tablet. Time required for 50% drug release and the disintegration time was linear	91

FUTURE PROSPECTS:

The colon has captured attention as a site for the delivery of drugs because of its greater responsiveness to absorption enhancers, protease inhibitors, and novel bioadhesive and biodegradable polymers. Although the success rate of these approaches, when used alone is pretty low, when used in combinations, these agents have demonstrated wonders in increasing the drug bioavailability. The development of a dosage form that

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improves the oral absorption of peptide and protein drugs whose bioavailability is very low because of instability in the GI tract (due to pH or enzymatic degradation) is one of the greatest challenges for oral peptide delivery in the pharmaceutical field. Colon targeted multiparticulate systems like microspheres and nanoparticles can provide a platform for spatial delivery of candidates like peptides, proteins, oligonucleotides and vaccines. The bioavailability of protein drugs delivered at the colon site needs to address. Studies on drug absorption by the intestinal system have focused on drug transporters that mediate drug influx and efflux and agents which can enhance drug absorption. The colon segment is designed by nature mainly to expel metabolism products rather than to absorb nutrients. Therefore, more research that is focused on the specificity of drug uptake at the colon site is necessary. Such studies will be significant in advancing the cause of colon targeted delivery of therapeutics in future.

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